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Do new generation stents improve PCI outcomes for unprotected left main disease when compared to CABG? A word of caution from a network meta-analysis of randomized controlled trials.

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Abbreviation lists

BioES: Biolimus eluting stent

BMS: bare metal stents

CABG coronary artery bypass graft

DES drug-eluting stents

EES: Everolimus eluting stent

MI myocardial infarction

PCI percutaneous coronary intervention

PES: paclitaxel-eluting stents (PES)

RCT randomized controlled trials

SES: sirolimus-eluting stents

LMD left main disease

ZES: zotarolimus-eluting stents

Central message: The introduction of new generation drug eluting stents for unprotected left main disease did not translated into better clinical outcomes compared to coronary artery bypass surgery.

Prospective statement: Whether the evolution of stents technology has translated into better results after percutaneous coronary intervention for unprotected left main disease remains unclear. The present network meta-analysis suggests that new generation stents are not associated with better outcomes when compared to coronary artery bypass surgery.

Abstract

Background: With the advent of bare metal stents (BMSs) and drug-eluting stents (DESs), percutaneous coronary intervention (PCI) has emerged as an alternative to coronary artery bypass graft (CABG) surgery for unprotected left main disease (LMD). However, whether the evolution of stents technology has translated into better results after PCI remains unclear. We aimed to compare CABG with stents of different generations for LMD by performing a Bayesian network meta-analysis (NMA) of available randomized controlled trials (RCT).

Methods: All RCTs with at least 1 arm randomized to PCI and/or CABG for LMD were included. Poisson methods and Bayesian framework was used to compute head-to-head incidence rate ratio (IRR) and 95% credible intervals (CrIs). Primary endpoint were the composite of death/myocardial infarction (MI)/stroke and repeat revascularization.

Results: Nine were included in the final analysis. Overall, 6 studies compared PCI and CABG (n=4,654) and other three compared different type of stents (n=1,360). Follow-up ranged from 6 moths to 5 years. BMS (IRR 0.63; 95%CrI 0.27-1.4) and 1st generation DES (IRR 0.85;9%%CrI 0.65-1.1) did not significantly differ from CABG for the composite of death/MI/stroke. Surprisingly, 2nd generation DES were associated with a significantly increase the risk of death/MI/stroke when compared to CABG (IRR 1.3; 95%CrI 1.1-1.6). Moreover, while 1st generation DES (IRR 1.8; 95%CI 1.4-2.4) narrowed the gap between CABG and PCI in terms of repeat revascularization when compared to BMS (HR 5.1; 95%CI 2.1-14), the risk of a further reintervention did not further improve with 2nd generation DES (IRR 1.8; 95%CI 1.4-2.4).

Conclusions: The introduction of new generation DES did not translate into better outcome from PCI when compared to CABG.

Introduction

Coronary artery bypass grafting (CABG) has long been considered superior to percutaneous coronary intervention (PCI) in the treatment of choice for unprotected left main disease (LMD)[1]. However, with the advent of bare metal stents (BMS) and first-generation drug eluting stents (DES) including paclitaxel-eluting stents (PES) and sirolimus-eluting stents (SES), PCI has emerged as an attractive alternative [1,2]. The recent introduction of second generation DES including everolimus-eluting stents (EES), and zotarolimus-eluting stents (ZES) and biodegradable polymer biolimus eluting stent (Bio-ES) has further promoted PCI in this setting[3].

However, whether the evolution of stents technology has translated into better results after PCI remains unclear. Despite the lack of definitive evidence on the equipoise between PCI with 2nd generation DES and CABG in terms of hard clinical endpoints, the current trend is preferring PCI to CABG when technically feasible.

We aimed to compare CABG with stents of different generations for LMD by performing a Bayesian network meta-analysis (NMA) of available randomized controlled trials (RCT).

Material and methods

This work was designed as a systematic review and network meta-analysis, with reporting following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement[4-6].

Data sources and searches

We searched PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE from their inception to November 2016, without language restrictions. Search algorithm used was "Left main" AND ("percutaneous coronary intervention" OR PCI OR stent*) AND ("coronary artery bypass" OR CABG OR "bypass surgery"

OR "coronary bypass"). Reference lists of the identified reports and relevant reviews were manually screened by 3 reviewers (UB, ADF, LBO) to identify further relevant studies. In addition, when other meta-analyses, systematic reviews, or RCTs were found, we used backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) to obtain further studies.

Study selection

Investigators first examined references at the title/abstract level, with divergences resolved by consensus, and then, if potentially pertinent, retrieved the complete articles. Articles were included in the present analysis if they fulfilled the following inclusion criteria: random allocation to treatment, at least 1 group randomized to CABG and/or PCI for LMD.

Data extraction and quality assessment

Baseline including SYNTAX score[7], procedural, outcome, and follow-up data were independently abstracted by 2 investigators. In the present analysis outcomes were adjudicated according to the original authors' definitions. Outcomes were analysed according to the intention-to-treat principle whenever possible. The internal validity and risk of bias of included trials were appraised by 2 independent investigators (U.B, M.K) according to the "risk of bias assessment tool" developed by the Cochrane collaboration[8]. Briefly, for each trial, 7 domains were assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data reporting, selective reporting, and presence of other bias. Presence of possible source of bias in each domain was assessed, and a final judgment of low, moderate, or high risk of bias was assigned.

Endpoints

Primary endpoint was the commonly adopted composite of death, myocardial infarction (MI) or stroke (death/MI/stroke) at longest follow-up available. As 2nd generation stents are anticipated to reduce the risk of restenosis, repeat revascularization was also considered a primary endpoint. Secondary endpoints were: mortality and MI.

Data synthesis and analysis

The network meta-analysis was conducted using R (version 3.2.0, R Project for Statistical Computing) with the gemtc and rjags packages, which interface with Just Another Gibbs Sampler (JAGS) software (version 3.4.0). Two separate analyses were conducted. The first analysis compared different stents generations against CABG and stents were categorized in three groups: BMS, 1st generation stents which included PES and SES and finally 2nd generation stents which included BioES, EES and ZES. The second analysis compared individual stents against CABG.

When modelling the clinical outcomes of interest, it is important to consider the different follow up times of the various trials, as longer follow up is likely to result in more reported events. To account for this, an underlying Poisson process with a constant event rate was assumed with total number of events observed within a treatment group out of the total person-time of follow-up for that treatment group calculated from study follow up. A log link function was used to model the incidence rate.

Relative effect estimates from the NMA were calculated as log incidence rate ratios (IRR) with 95% credible intervals (CrIs). For all practical purposes, incidence rates can be thought of as hazards and thus the IRR can be roughly interpreted as hazard ratio. Incidence of primary endpoints observed in each treatment arm for each included trial

was extracted and pooled using the Bayesian fixed effects model[9]. A fixed effects model was chosen because it had a lower deviance information criterion (DIC) compared to the random effects model, suggesting a better model fit. Non-informative prior distributions were chosen for model parameters so that results were driven entirely by the reported data. Analyses were performed using Markov-Chain Monte-Carlo methods, a method that estimates the effect of each treatment comparison by simulation, using four chains with 100,000 iterations and thinning interval of ten, after a burn-in of 50,000[9]. Convergence of the chains was assessed using the Gelman plot and diagnostic test[10]. Statistical significance was considered when the CrIs did not cross the line of no effect. The effect of SYNTAX score on treatment effect was investigated using meta-regression analysis as proposed by Gelman et al. [11]

Consistency

An assumption of NMA models is that direct and indirect sources of evidence estimate the same true treatment effect. This was evaluated by conducting conventional pairwise meta-analyses and testing consistency by comparing the direct and indirect evidence results to see if a statistically significant difference existed. We applied the back-calculation method to check for consistency within the evidence networks[12]. Based on the back-calculation method, the difference between direct and indirect estimate was considered as an estimate of inconsistency. Our null hypothesis was that there was consistency between the direct and indirect evidence and we would reject the null hypothesis if there was a statistically significant difference between the direct and indirect evidence comparison ($p<0.05$).

As secondary analysis, a pairwise meta-analysis was conducted to pool data from RCT comparing PCI versus CABG for primary endpoints with subgroup analysis according to type of stents used. We derived the log IRR and corresponding standard

error from numbers of reported events and accumulated person-years of follow-up. Finally log IRR were pooled using the generic inverse variance method with random and fixed model. Hypothesis of statistical heterogeneity was tested by means of Cochran Q test, with statistical significance set at the two-tailed 0.10 level, while extent of statistical consistency was measured with I^2, defined as 100% X (Q-df)/Q, where Q is Cochran's heterogeneity statistic and the degrees of freedom.

Results

Of 2597 potentially relevant articles initially screened, nine met the inclusion criteria and were included in the final analysis [1-3, 13-18] (Figure 1). Flow diagram of study selection is reported in Supplementary Figure 1. Overview of study characteristics in individual RCT is reported in Table 1 and Supplementary Table 1 and Supplementary Table 2. Internal validity assessment for each trial are reported in Supplementary Table 3. Overall, 6 studies[1-3,13-15] compared PCI and CABG (n=4,654) and other three[16-18] compared different type of stents (n=1,360). Follow-up ranged from 6 moths to 5 years.

Network meta-analysis

NMA estimates for primary and secondary endpoints are reported in Figure 2 and Figure 3 and Supplementary Table 4. BMS (IRR 0.63; 95%CrI 0.27-1.4) and 1st generation DES (IRR 0.85;9%%CrI 0.65-1.1) did not significantly differ from CABG for the composite of death/MI/stroke. Surprisingly, 2nd generation DES were associated with a significantly increase the risk of death/MI/stroke when compared to CABG (IRR 1.3; 95%CrI 1.1-1.6). This result was driven by a significantly increased risk of MI with BioES (IRR 3.0; 95%CrI 1.5-6.4), a non-significant excess of death and MI with ZES and a marginally non-significant increased risk of death with EES (IRR 1.4; 95%CrI 0.97-1.9).

We also found that while the introduction of 1st generation DES (IRR 1.8; 95%CI 1.4-2.4) narrowed the gap between CABG and PCI in terms of repeat revascularization when compared to BMS (HR 5.1; 95%CI 2.1-14), the risk of a further reintervention did not further improve with 2nd generation DES (IRR 1.8; 95%CI 1.4-2.4).

The comparison between CABG and different type of stents was constant across SYNTAX score values for both the composite of death/MI/stroke and repeat revascularization (Supplementary Figure 2 and 3). No inconsistency was found between direct and indirect comparison expect for a marginally significant difference for the composite of death/MI/stroke between BMS vs CABG and BMS vs PES (Supplementary Figure 4)

Pairwise meta-analysis PCI vs CABG

Pairwise comparison between PCI and CABG was based on 6 RCTs. Overall, PCI and CABG were comparable for death/MI/stroke (IRR 0.99; 95%CI 0.70-1.4). However, while 1st generation DES were associated with a non-significant 11% relative risk reduction of death/MI/stroke when compared to CABG, 2nd generation DES were associated with a 33% relative risk increase. Pairwise comparison confirmed that 1st generation DES (IRR 1.82; 95%CI 1.39-2.4) and 2nd generation DES (HR 1.79; 95%CI 1.42-2.2) presented comparable incidence rate ratio for repeat revascularization when compared to CABG.

Discussion

The main finding of the present NMA was that the introduction of 2nd generation DESs did not improve PCI outcomes when compared to CABG for unprotected LMD. Surprisingly 2nd generation DESs were associated with a significant trend towards an increased risk of death/MI/stroke when compared to CABG while this was not observed with BMS or 1st generation stents (SES and PES). When outcomes from

individual stents were analysed separately, we found that BioES was associated with a significant 3-fold increased risk of MI, ZES showed a non-significant trend towards increased risk of mortality and MI and EES showed a marginally non-significant increased risk of mortality.

Finally, we found that while the introduction of 1st generation DESs narrowed the gap between CABG and PCI in terms of repeat revascularization when compared to BMS, the risk of a further reintervention did not further improve with 2nd generation DESs.

Concern about the long-term safety of DESs for unprotected LMD disease has been raised in the past due to the observed risk of stent thrombosis which may outweigh the benefits of DESs [19-21]. Despite the SYNTAX trial[3] and the PRECOMBACT trail[9] has shown comparable results between first generation DESs and CABG for unprotected LMD, these studies were largely underpowered to detect difference in hard clinical endpoints such as death and MI. New generation DES including polymer BioES and EES and have been introduced to replace first generation DES with more biocompatible and thinner polymers to reduce of stent thrombosis rates[21]. However, two recent large RCTs, NOBLE[1] and EXCEL[2], compared BioES and EES respectively versus CABG reaching conflicting conclusions about the non-inferiority of PCI over CABG. Such a discrepancy can be partially related to different definitions adopted for MI. In fact, for the primary endpoint definition, the NOBLE trail included non-procedural MI only while EXCEL, SYNTAX and PRECOMBAT included both procedural and subsequent spontaneous MI. However, PCI-related MI has a greater impact on long term prognosis than CABG-related MI and there is still controversy on which unifying common definition for PCI-related and CABG-related MI should be adopted[22]. This aspect calls into question the validity of endpoints definitions which include peri-procedural MI in the comparison between PCI and CABG. Of notice, in EXCEL, while

the two strategies did not differ for the composite of procedural and spontaneous MI, PCI was associated with an increased risk of subsequent spontaneous MI when compared to CABG.

Second generation DESs including EES and BioES have been developed to improve PCI outcomes achieved with 1st generation DESs by reducing the risk of stent thrombosis and restenosis and several investigations have confirmed their efficacy[23]. However, it must be noticed that in the vast majority of these studies, 2nd generation DESs have been used to treat distal targets. We can speculate that the superiority of 2nd generation over 1st generations DESs might not be reproducible in LMD. It has been shown that the risk of restenosis might be less relevant in case of coronary arteries with larger diameter (≥ 3.5 mm)[24] and this aspect can partially explain the lack of benefit in terms of repeat revascularization with 2nd generation DES observed in the present NMA.

On the other hand, BioESs have been perceived as safer than 1st generation DESs, mainly on the basis of results from individual trials powered only for composite endpoints of safety and efficacy[25]. However, a recent landmark NMA[26] concluded that BioES is associated with an excess of death and MI when compared to other durable polymer DESs. Biodegradable polymer DESs such as BioES employs polymers that dissolve after time in which antiproliferative drug elution is needed. Once the degradation process of the polymer is completed in these devices, what remains is a bare-metal scaffold with thick-struts design. This platform may provide lower elasticity than durable polymers, with an increased risk of fragility and micro-damage to the coating, and potential “jailing” of side branches. these factors explain the lower safety profile with biolimus biodegradable polymer stents[26].

As with any meta-analysis, our report shares the limitations of the original studies. By exploiting potentially complex evidence networks along with indirect and direct comparisons, network meta-analysis assumes that patients enrolled in the component studies were sampled from the same theoretical population and that similar comparators between different trials have a consistent risk-benefit ratio.

In the present analysis, some studies have a limited sample size and there was a relatively small number of trials for the comparison of individual stents against CABG. As a consequence, few comparisons present relatively wide confidence interval (unaddressed uncertainty). However, no inconsistencies were apparent between the direct and indirect estimates for the endpoints considered across all comparisons, which provides strong scientific support for the reliability of the network. Results were analysed on aggregate data, and therefore, we could not assess whether all baseline characteristics were balanced between the groups. Finally, several comparisons were of borderline statistical significance, and even greater numbers of patients with longer-term follow-up would add greater precision to the present results.

In conclusion, a word of caution should be exercised on the current trend of preferring PCI with new generation DESs over CABG for LMD in view of the present findings. We did not demonstrate the anticipated benefit from 2nd generation DESs in this population in terms of mortality, MI and repeat revascularization. The routine use of new generation DESs in the treatment of LMD still deserves further investigations. Current trials are largely underpowered to clarify whether DESs are as safe as CABG in terms of mortality and the use of endpoints including procedural MI might have masked potential risks with DESs. Adequately powered and well-designed studies are needed to guide clinician in decision making. Finally concerns remain as most of

clinical research studies are funded by manufacturers with the relative risk of bias in favour of a new devices.

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Table 1. Characteristics of randomized controlled trials included in the network meta-analysis

Trial	Year	Treatment received	EuroSCORE (PCI)	EuroSCORE (CABG)	SYNTAX (PCI)	SYNTAX (CABG)	Not isolated LMD, %	Distal LMD, %	Follow-up (years)
NOBLE	2016	CABG vs Bio-ES	2 (2, 4)	2 (2, 4)	22.5±7.5	22.4±8.0	NA	81	3.1
EXCEL	2016	CABG vs EES	NA	NA	26.9±8.8	26.0±9.8	82.2	79.2	3
LE MANS	2016	CABG vs BMS	3.3±2.3	3.5±2.3	25.2±8.7	24.7±6.8	94	60	1
PRECOMBAT	2015	CABG vs SES	2.6±1.8	2.8±1.9	24.4±9.4	25.8±10.5	NA	67	5
SYNTAX	2014	CABG vs PES	3.9±2.8	3.9±2.9	29.6±13.5	30.2±12.7	85.9	58.3	5
Boudriot, et al	2011	CABG vs SES	2.4 (1.5, 3.7)	2.6 (1.7, 4.9)	24.0 (19.0, 29.0)	23.0 (14.8, 28.0)	71	69	1
Erglis et al.	2007	BMS vs PES	NA	-	32.6±11.7	-	49	75%	0.5
ISAR-LEFT-MAIN	2009	PES vs SES	4.7±3.4	-	NA	-	NA	64%	1
ISAR-LEFT-MAIN 2	2013	ZES vs EES	5.1 ± 3.7		NA	-	NA	79%	1

Values are mean, median (interquartile range), or %. PCI: percutaneous coronary intervention; CABG = coronary artery bypass graft surgery; FU = follow-up; LMD = left main disease;; NA = not available;BioES: Biolimus eluting stent; BMS: bare metal stents; EES: Everolimus eluting stent; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stent

Expanded study abbreviations are as follows: EXCEL = the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; LE MANS = Study of UnprotectedLeft Main Stenting Versus Bypass Surgery; NOBLE = The Nordic-Baltic-British left main revascularisation study; PRECOMBAT = the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX = the other Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions

11 **Supplementary Table 1.** Main inclusion and exclusion criteria, primary and secondary endpoints of randomized controlled trials.

Trial	Main inclusion criteria	Main exclusion criteria	Primary endpoint	Secondary endpoint
NOBLE	stable angina pectoris, unstable angina pectoris, or acute coronary syndrome, together with a lesion with visually assessed stenosis diameter ≥50% or fractional flow reserve ≤0·80 in the left main coronary artery ostium, mid-shaft, or bifurcation, with no more than three additional noncomplex lesions.	ST-elevation infarction within 24 h, being considered too high risk for CABG or PCI, or expected survival of less than 1 year.	Composite of major adverse cardiac and cerebrovascular events (MACCE; death from any cause, non-procedural myocardial infarction, repeat revascularisation, or stroke).	The individual component of the primary MACCE endpoint, definite stent thrombosis, and symptomatic graft occlusion. Procedural myocardial infarctions were documented (post hoc). Repeat revascularisations.
EXCEL	Stenosis of the left main coronary artery of 70% or more, as estimated visually, or stenosis of 50% to less than 70% if determined by means of noninvasive or invasive testing to be hemodynamically significant, and a consensus among the members of the heart team regarding eligibility for revascularization with either PCI or CABG. In addition, participants were required to have low-to-intermediate anatomical complexity of coronary artery disease, as defined by a site-determined SYNTAX score of 32 or lower (the SYNTAX score reflects a comprehensive angiographic assessment of the coronary vasculature, with 0 as the lowest score and higher scores [no upper limit] indicating more complex coronary anatomy).	Prior PCI of the left main trunk at any time prior to randomization, PCI of any other (non-left main) coronary artery lesions within one year prior to randomization, CABG at any time prior to randomization. Need for any concomitant cardiac surgery other than CABG. Angiographic exclusion criteria: a. Left main diameter stenosis <50%, unless left main equivalent disease is present; b. SYNTAX score ≥33, as determined by the local Heart Team; c. Visually estimated left main reference vessel diameter <2.25 mm or >4.25 mm d. The presence of specific coronary lesion characteristics or other cardiac condition(s) which leads the participating interventional cardiologist or cardiac surgeon to believe that clinical equipoise is not present	the primary composite end point of death from any cause, stroke, or myocardial infarction	a composite of death from any cause, stroke, or myocardial infarction at 30 days and the rate of a composite of death, stroke, myocardial infarction, or ischemia-driven revascularization at 3 years. Additional secondary end points included the components of the primary end point, as well as revascularization, stent thrombosis, symptomatic graft stenosis or occlusion, bleeding complications, and a prespecified composite of periprocedural major adverse events.

LE MANS	Patients with >50% narrowing of ULMCA, with or without multivessel coronary artery disease suitable for equal revascularization both with PCI and CABG. All patients had to be symptomatic with documented myocardial ischemia.	Acute myocardial infarction, total occlusion of left main, comorbid conditions, or coronary anatomic considerationsthat increased the surgical risk to a Euroscore of 8 or more, stroke or transient ischemic attack within 3 months, renal dysfunction, or contraindication to antiplatelet therapy.	The change in LVEF assessed by 2-dimensional echocardiography 12 months	MACCE (Major adverse cardiac and cerebrovascular events), MAE (other major adverse events) length of hospitalization, exercise tolerance measured with an electrocardio graphic treadmill stress test along with angina severity according to the Canadian Cardiovascular Society classification after 1 year, total survival, target vessel failure (TVF) and revascularization (TVR).
PRECOMBAT	Older than 18 years of age and had received a diagnosis of stable angina, unstable angina, silent ischemia, or non–ST-segment elevation MI. All patients had newly diagnosed ULMCA stenosis (more than 50% diameter stenosis by visual angiographic estimation) and had been judged to be suitable candidates for either PCI or CABG.	Systemic (intravenous) sirolimus use within 12 months. Any previous percutaneous coronary intervention (PCI) within 1 year. Previous bypass surgery. Any previous PCI of a ULMCA or ostial left circumflex artery or ostial left anterior descending artery lesion within 1 year. Acute MI within 1 week. Ejection fraction <30%. Cardiogenic shock.	Composite of death from any cause, MI, stroke, or ischemia-driven target vessel revascularization [TVR])	The individual components of the primary endpoint; a composite of death, MI, or stroke; and clinically driven TVR.
SYNTAX	De novo lesions, ≥50% target vessel stenosis with stable/unstable angina or atypical chest pain. If asymptomatic, positive evidence of myocardial ischemia was required.	Previous PCI or CABG, acute myocardial infarction (MI), or the need for concomitant cardiac surgery.	Composite of major adverse cardiac and cerebrovascular events (i.e., death from any cause, stroke, myocardial infarction, or repeat revascularization)	The individual component of the primary MACCE endpoint, Quality of life and costeffectiveness.

Boudriot, et al	Patients age 18 to 80 years with stenosis (>50%) of the ULM with or without additional multivessel coronary artery disease were included in this multicenter study. Patients had to be symptomatic or have documented myocardial ischemia.	Myocardial infarction48 h requiring immediate intervention, additional valvular heart disease requiring surgery, previous surgical treatment for coronary artery or valvular disease, severe peripheral arterial disease, significant carotid stenosis requiring treatment, renal dysfunction requiring dialysis, any disease with limited life expectancy, overt congestive heart failure, and contraindication to antiplatelet therapy. Angiographic exclusion criteria were total occlusions, extreme left-dominant coronary artery perfusion, and distal lesion length >30 mm in a single lesion	Major adverse cardiovascular events, which included death from any cause, myocardial infarction, and the need for repeat revascularization	Each individual component of the composite end point.
Erglis et al.	Eligible patients were those with clinically symptomatic LM disease with angiographic evidence of.>50% diameter stenosis of LM suitable for stent implantation. All patients were good candidates for CABG.	CABG to left anterior descending (LAD) artery branches or left circumflex (LCX) branches	neointimal growth (volume, square, luminal diameter, and late lumen loss) evaluated by IVUS at 6 months, or earlier if clinically indicated.	Major adverse cardiac events (MACE) were defined as death, myocardial infarction (MI), and target lesion revascularization (TLR)
ISAR-LEFT-MAIN	patients older than age 18 years with ischemic symptoms or evidence of myocardial ischemia in the presence of >50% de novo stenosis located in the left main stem	ST-segment elevation myocardial infarction (MI) within 48 h of symptom onset; prior bypass graft surgery; in-stent restenosis; cardiogenic shock; malignancies or other comorbid conditions with life expectancy <1 year or that might result in protocol noncompliance; left main size >4.5 mm; planned staged PCI procedure within 30 days from index PCI; planned elective surgical procedure necessitating interruption of clopidogrel during the first 6 months after enrollment; known allergy to the study medications: clopidogrel, rapamycin, paclitaxel, stainless steel, or cobalt alloy; pregnancy; or previous enrollment in this trial	the combined incidence of death, myocardial infarction, and target lesion revascularization (TLR) at 1 year	angiographic restenosis on the basis of the LMCA area analysis at follow-up angiography

ISAR-LEFT-MAIN 2	patients older than 18 years of age with ischemic symptoms or evidence of myocardial ischemia in the presence of >50% de novo stenosis located in the left main stem	ST-segment elevation MI within <48 h of symptom onset; prior CABG surgery; in-stent restenosis; cardiogenic shock; malignancies or other comorbid conditions with a life expectancy <1 year; planned staged PCI procedure within 30 days of index PCI; planned elective surgical procedure necessitating interruption of P2Y12-receptor inhibitors during the first 6 months post-enrollment; known allergy to the study medications: everolimus, zotarolimus, or cobalt alloy; pregnancy; or previous enrollment in this trial	combined incidence of death, myocardial infarction, and target lesion revascularization	definite or probable stent thrombosis at 1 year and angiographic restenosis based on analysis of the left main coronary artery area at follow-up angiography

Expanded study abbreviations are as follows: : EXCEL = the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; LE MANS = Study of UnprotectedLeft Main Stenting Versus Bypass Surgery; NOBLE = The Nordic-Baltic-British left main revascularisation study; PRECOMBAT = the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX = the other Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions

18 **Supplementary Table 2.** Outcome definition in randomized controlled trials.

NOBLE (The Nordic-Baltic-British left main revascularisation study)

All–cause mortality: Death from any cause.

Cardiac death: Cardiac death was defined as any death due to a suspected cardiac cause (myocardial infarction, low–output heart failure, fatal arrhythmia), unwitnessed death and death of unknown cause. All procedure–related deaths, including those related to concomitant treatment, were classified as cardiac death. The endpoint was included post hoc. (Modified from Cutlip et al. Circulation. 2007;115:2344–2351) The information on cause of death was obtained from hospital patient files, from general practitioners, or from families if no other source was available.

Vascular death: Death caused by non–coronary vascular causes, including cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular diseases. The endpoint was included post hoc. (Modified from Cutlip et al. Circulation. 2007;115:2344–2351)

Non–procedure–related myocardial infarction: A rise in biochemical markers exceeding the decision limit for myocardial infarction (99th percentile including < 10% CV) with at least one of the following; (1) ischemic symptoms, (2) ECG changes indicative of ischemia (ST segment elevation or depression), and (3) development of a pathologic Q–wave with no relation to a PCI procedure.

Repeat revascularization: Any new PCI or CABG operation performed during follow–up. If an index revascularisation was attempted or successful, any subsequent revascularisation was counted as repeat revascularisation. Attempted PCI was defined as an advancement of a wire in the coronary tree at least. Attempted CABG was defined as at least initiation of an index operation.

Procedure–related biomarker release: The diagnosis of a procedure–related biomarker increase required a rise in total creatine kinase (CK) and/or Troponin–T/I. Due to the great heterogeneity of biomarkers and various assays used during the study in participating centres, this comparison was omitted from the final analysis.

Procedural myocardial infarction: Diagnosis of procedural MI for both PCI and CABG patients was based on CK–MB elevations when available. Patients needed to have stable angina pectoris as the clinical indication OR a normal baseline CK–MB, TnI, TnT, or highly sensitive TnT, to be assessable for procedural MI. Diagnosis required a CK–MB value above 10 x URL or ULN to establish the diagnosis. The diagnosis could also be placed by the combination of a CK–MB value above 5 x URL or ULN, AND one or more of the following: (1) new pathological Q waves in at least 2 contiguous leads or new persistent non–rate–related left bundle branch block, or (2) angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. The endpoint of procedural myocardial infarction was included post hoc and the definition was adapted to match the definition applied in the EXCEL trial on PCI vs. CABG for LMCA stenosis. Peri-procedural MI due to repeat revascularization during follow-up were assessed applying the 3rd Universal definition as CK-MB was not available in all event patients. A procedural MI according to this definition was counted as a non-index procedural myocardial infarction.

Non-procedural myocardial infarction: Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012; 126: 2020–35.

Target lesion revascularization: Repeat revascularisation by PCI of any target segment treated during the index procedure. A target lesion segment was defined as a stented or balloon treated segment and its 5 mm margins.

LMCA revascularization: Any subsequent revascularisation by PCI of the segments within 5 mm of any treated segment related to the LMCA or the LMCA bifurcation. Any revascularisation by CABG of native LMCA including the LMCA bifurcation, or revascularisation of a graft supplying the left anterior descending artery or circumflex arteries.

Definite stent thrombosis: Stent thromboses were categorized as acute, subacute, late and very late and as definite, probable and possible according to ARC criteria. (Cutlip et al. Circulation 2007;115:2344–51)

Symptomatic graft occlusion: Diagnosis of symptomatic graft occlusion required it to be detected during a clinically indicated coronary angiography.

Stroke: Ischemic or haemorrhagic cerebrovascular event verified by brain computed tomography (CT) or magnetic resonance imaging (MRI).

Pulmonary embolus: The diagnosis of pulmonary embolus required verification by an appropriate computed tomography scan.

EXCEL (the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial)

Death: The cause of death will be adjudicated as being due to cardiovascular causes, non-cardiovascular causes, or undetermined causes.

Cardiovascular death includes sudden cardiac death, death due to acute MI, heart failure or cardiogenic shock, stroke, other cardiovascular causes, or bleeding

Non-cardiovascular death is defined as any death with known cause not of cardiac or vascular causes

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a noncardiovascular cause. For this trial all deaths of undetermined cause will be included in the cardiovascular category

Myocardial infarction (protocol definition):

Post procedure MI: Defined as the occurrence within 72 hours after either PCI or CABG of either:

CK-MB >10x upper reference limit (URL)*, OR

CK-MB >5x URL*, PLUS

-new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, or

-angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or

-imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Spontaneous MI: defined as the occurrence >72 hours after any PCI or CABG of:

The rise and/or fall of cardiac biomarkers (CK-MB or troponin) >1x URL* PLUS:

- ECG changes indicative of new ischemia [ST -segment elevation or depression, in the absence of other causes of ST -segment changes such as left ventricular hypertrophy (LVH) or bundle branch block (BBB)], or
- Development of pathological Q waves (≥0.04 seconds in duration and ≥1 mm in depth) in ≥2 contiguous precordial leads or ≥2 adjacent limb leads) of the ECG, or
- Angiographically documented graft or native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Each MI will also be adjudicated as:

- ST-segment elevation MI (STEMI)
- Non-ST-segment elevation MI (NSTEMI)
- Each STEMI and NSTEMI will be subcategorized as
  - -Q-wave
  - -Non-Q-wave
  - -Unknown (no ECG or ECG not interpretable)

Stroke: The rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). A vascular neurologist or stroke specialist will determine whether a stroke has occurred and determine the stroke severity using the NIHSS TIA/Stroke questionnaire. Available neuroimaging studies will be considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes will be classified as ischemic, hemorrhagic, or unknown. Four criteria must be fulfilled to diagnosis stroke:

1. Rapid onset of a focal/global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia/aphasia, hemianopia, amaurosis fugax, other new neurological sign(s)/symptom(s) consistent with stroke; and
2. Duration of a focal/global neurological deficit ≥24 hours or <24 hours if any of the following conditions exist:
   i. At least one of the following therapeutic interventions:
      a. Pharmacologic (i.e., thrombolytic drug administration)
      b. Non-pharmacologic (i.e., neurointerventional procedure such as intracranial angioplasty)
   ii. Available brain imaging clearly documents a new hemorrhage or infarct
   iii. The neurological deficit results in death
3. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, other metabolic abnormality, peripheral lesion, or drug side effect). Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
4. Confirmation of the diagnosis by a neurology or neurosurgical specialist and at least one of the following:
   a. Brain imaging procedure (at least one of the following):
      i. CT scan
      ii. M RI scan
      iii. Cerebral vessel angiography
   b. Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

All strokes with stroke disability of modified Rankin Scale (mRS) ≥1 (increase from baseline assessment) will be included in the primary endpoint. All diagnosed strokes (even with mRS 0) will also be tabulated.

Ischemia-driven revascularization:

A coronary revascularization procedure may be either a CABG or a PCI. The coronary segments revascularized will be sub-classified as:

 Target Lesion: A lesion revascularized in the index procedure (or during a planned or provisional staged procedure). The LM target lesion extends from the left main stem ostium to the end of the 5 mm proximal segments of the left anterior descending and left circumflex arteries as well as the ramus intermedius if the latter vessel has a vessel diameter of ≥2 mm.

 Target Vessel: The target vessel is defined as the entire major coronary vessel proximal and distal to the target lesion including upstream and downstream branches and the target lesion itself. The left main and any vessel originating from the left main coronary artery or its major branches is, by definition, considered a target vessel for the purposes of this trial (unless either the LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG).

 Target Vessel Non-Target Lesion: The target vessel non-target lesion consists of a lesion in the epicardial vessel/branch/graft that contains the target lesion; however, this lesion is outside of the target lesion by at least 5 mm distal or proximal to the target lesion determined by quantitative coronary angiography (QCA).

 Non-Target Vessel: For the purposes of this trial, the only possible non-target vessel would be the right coronary artery and its major branches that were not treated by either PCI or CABG at the index procedure (unless either the LAD or LCX are occluded at baseline and no attempt was made to revascularize these territories by either PCI or CABG).

All revascularization events will be adjudicated as either ischemia -driven or non-ischemia -driven. Revascularization will be considered ischemia driven if the diameter stenosis of the revascularized coronary segment is ≥50% by QCA and any of the following criteria for ischemia are met:

- •A positive functional study corresponding to the area served by the target lesion; or
- •Ischemic ECG changes at rest in a distribution consistent with the target vessel; or
- •Typical ischemic symptoms referable to the target lesion; or
- •IVUS of the target lesion with a minimal lumen area (MLA) of ≤4 mm^2 for non-left main lesions or ≤6 mm^2 for left main lesions. If the lesions are de novo (i.e. not restenotic), the plaque burden must also be ≥60%; or
- •FFR of the target lesion ≤0.80

A target lesion revascularization for a diameter stenosis less than 50% might also be considered ischemia-driven by the Clinical Events Committee if there was a markedly positive functional study or ECG changes corresponding to the area served by the target lesion.

Peri-procedural major adverse events:

The composite rate of any of the following, occurring within 30 -days post procedure

- •Death
- •Stroke
- •Myocardial infarction
- •Ischemia -driven revascularization
- •TIMI major or minor bleeding
- •Transfusion ≥2 units of blood
- •Major arrhythmia (supraventricular tachycardia requiring cardioversion, ventricular tachycardia or fibrillation requiring treatment, or bradyarrhythmia requiring temporary or permanent pacemaker)
- •Any unplanned surgery or therapeutic radiologic procedure
- •Renal failure (serum creatinine increase by ≥0.5 mg/dL from baseline or need for dialysis)
- •Sternal wound dehiscence
- •Infection requiring antibiotics
- •Prolonged intubation (>48 hours)
- •Post-pericardiotomy syndrome

LE MANS (Study of UnprotectedLeft Main Stenting Versus Bypass Surgery)

The major adverse events (MAE) were defined as all-cause mortality, acute myocardial infarction (defined as an increase in creatine phosphokinase (CPK)-MB to higher than 3 times the upper limit of normal after PCI and 5 times after CABG), repeat revascularization, acute heart failure (e.g., pulmonary edema, cardiogenic shock), or low output syndrome requiring intravenous inotropic agents and/or intra-aortic balloon pump support, post-procedural complications leading to reintervention, stroke, arrhythmia (ventricular fibrillation, ventricular

tachycardia, or atrial fibrillation), major bleeding requiring additional blood transfusion, and infections compromising post-procedural rehabilitation. Any cardiac mortality, acute myocardial infarction, stroke, repeat intervention, and/or acute/subacute in-stent thrombosis were considered MACCE.
Target vessel failure was defined as any MACCE related to insufficient flow through the LMCA, and TVR as any repeat intervention (PCI or CABG) caused by a narrowing of the LMCA. The incidence of stent thrombosis was evaluated in accordance with the Academic Research Consortium Definitions of Stent Thrombosis

SYNTAX (The other Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial)

Deaths were considered cardiac unless an unequivocal, noncardiac cause was established.
CVA was defined as a focal, central neurological deficit lasting >72 hours (h) which resulted in irreversible brain damage or body impairment.
Repeat revascularization was defined as any repeat PCI or CABG. Complete revascularization was defined as the successful treatment of all eligible lesions identified during the Heart Team conference and estimated post procedure by the investigator.
MI was based on previous studies, MI was defined in relation to intervention status as follows i) after allocation but before treatment: Q -wave (new pathological Q-waves in ≥2 leads lasting ≥0.04 seconds with CK-MB levels elevated above normal), and non-Q wave MI (elevation of CK levels >2 times the upper limit of normal [ULN] with positive CK-MB or elevation of CK levels to >2 times ULN without new Q-waves if no baseline CK-MB was available); ii) <7d after intervention: new Q-waves and either peak CK-MB/total CK >10% or plasma level of CK-MB 5x ULN; iii) 7d after intervention: new Q waves or peak CK-MB/total CK >10% or plasma level of CK-MB 5x ULN or plasma level of CK 5x ULN. The CK/CK-MB enzyme levels were obtained and measured by a core laboratory for all randomized patients.
Per protocol graft occlusion (GO) and stent thrombosis (ST) were considered acute if occurring ≤24h following the study procedure, sub-acute if occurring >24h to ≤30d following the study procedure and late after 30d. Per protocol graft occlusion and stent thrombosis were defined as either: i) clinical presentation of an acute coronary syndrome with documentation of a flow limiting thrombus or occlusion within a bypass graft or adjacent to the anastomosis of a previously bypassed coronary artery (for CABG patients) or within or adjacent to a previously successfully treated artery (for PCI patients); ii) a Q-wave MI in the territory of ≥1 treated vessels within first 30 days (d).

Boudriot, et al

Myocardial infarction was defined as an increase increatine kinase-MB activity >3 times the upper limit of normal after PCI and >5 times after CABG. In addition, standard electrocardiographic criteria were applied.
The incidence of stent thrombosis was evaluated in accordance with the Academic Research Consortium definitions.
Repeat revascularization was defined as anyrevascularization by CABG or PCI within 12 months, and was subdivided into target lesion revascularization of the ULM and distally located lesions or those of the right coronary artery.

Erglis et al.

Major adverse cardiac events (MACE) were defined as death, myocardial infarction (MI), and target lesion revascularization (TLR). Patients with more than 1 event were assigned the highest rank event.
All deaths were considered to be of cardiac origin unless a noncardiac origin was diagnosed.
Myocardial infarction (MI) was diagnosed by elevation of myocardial damage biomarkers: 3-fold in troponin I and 5-fold in MB fraction of creatine kinase.
Target lesion revascularization was defined as a repeat intervention (surgical or percutaneous) to treat a luminal stenosis in the stent or within the 5-mm segments adjacent to the stent, including the ostium of the LAD artery and/or LCX artery.

ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions)

The diagnosis of MI required the presence of new significant Q waves on the electrocardiogram and/or elevation of CK-myocardial band isoform (or CK if the latter was not available) at least 2 times the upper limit of normal in no fewer than 2 blood samples.
The TLR was defined as any repeat PCI involving the left main area or CABG involving at least 1 of the main left coronary vessels due to luminal renarrowing in the presence of symptoms or objective signs of ischemia.
Stent thrombosis was defined according to Academic Research Consortium criteria (Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344 –51.).
Angiographic binary restenosis was defined as diameter stenosis >50%, measured by quantitative coronary angiography, in the left main area.

ISAR-LEFT-MAIN 2 (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions 2)

The diagnosis of MI required the presence of new significant Q waves on electrocardiography and/or elevation of creatine kinase-MB isoform (or creatine kinase if the latter was not available) to at least 2 times the upper limit of normal in no fewer than 2 blood samples.

Target lesion revascularization (TLR) was defined as any repeat PCI involving the left main area or CABG surgery involving at least one of the main left coronary vessels due to luminal renarrowing in the presence of symptoms or objective signs of ischemia.

Stent thrombosis was defined according to Academic Research Consortium criteria (Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344 –51).

Angiographic binary restenosis was defined as diameter stenosis >50%, measured by quantitative coronary angiography, in the left main area.

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21 **Supplementary Table 3.** Risk of bias of included randomized controlled trials.

NOBLE		
Risk of bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated using permuted random blocks
Allocation concealment (selection bias)	Low risk	Web-based computer randomization
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Unclear risk	Over 20% losses (31% losses to follow-up)
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Unclear risk	the primary endpoint timing changed
EXCEL		
Risk of bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Variable block random allocation
Allocation concealment (selection bias)	Low risk	Interactive voice-based or Web-based system
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	8% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Study protocol is available, all expected outcomes included
Other bias	Low risk	Free of other sources of bias
LE MANS		
Risk of bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization stated to have been done but no method reported
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Blinded outcome assessors
Incomplete outcome data (attrition bias)	Low risk	11.4% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Include all expected outcomes
Other bias	Low risk	Free of other sources of bias
PRECOMBAT		
Risk of bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence
Allocation concealment (selection bias)	Low risk	Sealed envelopes concealed the allocation
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	6.8% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Study protocol is available, all expected outcomes included
Other bias	Low risk	Free of other sources of bias
SYNTAX		
Risk of bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Variable block random allocation
Allocation concealment (selection bias)	Low risk	Central allocation (Interactive Voice Response System)
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Outcome assessors blinded
Incomplete outcome data (attrition bias)	Low risk	5.2% of participants were lost to follow-up; reasons reported
Selective reporting (reporting bias)	Low risk	Study protocol is available, all expected outcomes included
Other bias	Low risk	Free of other sources of bias
Boudriot, et al		
Risk of bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized randomization program
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation was not reported
Blinding of participants and personnel (performance bias)	High risk	Blinding not applicable
Blinding of outcome assessment (detection bias)	Low risk	Blinded outcome assessors
Incomplete outcome data (attrition bias)	Low risk	0.5% of participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes included
Other bias	Low risk	Free of other sources of bias
Erglis et al.		
Risk of bias		
Random sequence generation (selection bias)	Unclear	No sufficient information to allow judgement
Allocation concealment (selection bias)	Unclear	No sufficient information to allow judgement
Blinding of participants and personnel (performance bias)	Unclear	No sufficient information to allow judgement
Blinding of outcome assessment (detection bias)	Unclear	No sufficient information to allow judgement
Incomplete outcome data (attrition bias)	Low risk	No patient lost to follow-up
Selective reporting (reporting bias)	Unclear	No sufficient information to allow judgement

Other bias	Low risk	There is no evidence of other bias
ISAR-LEFT-MAIN		
Risk of bias		
Random sequence generation (selection bias)	Low risk	Computer-generated sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias)	High-risk	The manuscript doesn't report information about the blinding of participants and personnel. We assume this is an open-label study
Blinding of outcome assessment (detection bias)	Low risk	An events committee blinded to treatment allocation adjudicated all adverse clinical events.
Incomplete outcome data (attrition bias)	Low risk	No patient lost to follow-up
Selective reporting (reporting bias)	Unclear	No sufficient information to allow judgement
Other bias	High-risk	The ISAR-LEFT-MAIN study was supported in part by an unrestricted grant from Cordis.
ISAR-LEFT-MAIN 2		
Risk of bias		
Random sequence generation (selection bias)	Low risk	Randomisation was done by a web-based computer randomisation system
Allocation concealment (selection bias)	Low-risk	Patients were assigned to the allocated treatment according to randomisation by the local research team.
Blinding of participants and personnel (performance bias)	High- risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study
Incomplete outcome data (attrition bias)	High-risk	17 patients lost to follow-up, unlikely to have influenced results
Selective reporting (reporting bias)	Unclear	No sufficient information to allow judgement
Other bias	Low-risk	Aarhus University Hospital was the main sponsor of the trial. Biosensors provided an institutional research grant for the trial but had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of this report; or in the decision to submit the paper for publication.

Expanded study abbreviations are as follows: : EXCEL = the Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial; LE MANS = Study of UnprotectedLeft Main Stenting Versus Bypass Surgery; NOBLE = The Nordic-Baltic-British left main revascularisation study; PRECOMBAT = the Premier of Randomized Comparison of Bypass Surgery versus Angioplasty Using Sirolimus-Eluting Stent in Patients with Left Main Coronary Artery Disease trial; SYNTAX = the other Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial. ISAR-LEFT-MAIN (Intracoronary Stenting and Angiographic Results: Drug-Eluting Stents for Unprotected Coronary Left Main Lesions

Supplementary Table 4. Full Network meta-analytic estimates (expressed as log incidence rate ratio, IRR and 95% credible interval; statistical significance in bold) (BioES: Biolimus eluting stent; BMS: bare metal stents; CABG: coronary artery bypass grafting; EES: Everolimus eluting stent; MI: myocardial infarction; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stent)

BioES	-1.166 (-3.262, 0.5108)	-0.1185 (-0.6011, 0.3578)	0.1858 (-0.4146, 0.7829)	-0.3287 (-0.9366, 0.2736)	-0.3186 (-0.9935, 0.3468)	0.192 (-0.7034, 1.083)	Mortality
1.166 (-0.5108, 3.262)	BMS	1.042 (-0.5564, 3.093)	1.348 (-0.2925, 3.43)	0.833 (-0.7845, 2.895)	0.843 (-0.8156, 2.939)	1.363 (-0.4249, 3.532)	
0.1185 (-0.3578, 0.6011)	-1.042 (-3.093, 0.5564)	CABG	0.3038 (-0.05129, 0.6653)	-0.2084 (-0.5795, 0.1597)	-0.1997 (-0.6654, 0.2652)	0.311 (-0.4428, 1.063)	
-0.1858 (-0.7829, 0.4146)	-1.348 (-3.43, 0.2925)	-0.3038 (-0.6653, 0.05129)	EES	-0.514 (-1.029, 0.0007923)	-0.505 (-1.093, 0.08261)	0.007237 (-0.659, 0.6691)	
0.3287 (-0.2736, 0.9366)	-0.833 (-2.895, 0.7845)	0.2084 (-0.1597, 0.5795)	0.514 (-0.0007923, 1.029)	PES	0.009336 (-0.4756, 0.4963)	0.5207 (-0.3156, 1.358)	
0.3186 (-0.3468, 0.9935)	-0.843 (-2.939, 0.8156)	0.1997 (-0.2652, 0.6654)	0.505 (-0.08261, 1.093)	-0.009336 (-0.4963, 0.4756)	SES	0.512 (-0.371, 1.397)	
-0.192 (-1.083, 0.7034)	-1.363 (-3.532, 0.4249)	-0.311 (-1.063, 0.4428)	-0.007237 (-0.6691, 0.659)	-0.5207 (-1.358, 0.3156)	-0.512 (-1.397, 0.371)	ZES	
BioES	-0.7653 (-2.094, 0.5427)	**-1.087 (-1.864, -0.3979)**	**-1.148 (-1.983, -0.3826)**	-0.7197 (-1.647, 0.1613)	-0.8682 (-1.881, 0.1073)	-0.2824 (-1.7, 1.26)	MI
0.7653 (-0.5427, 2.094)	BMS	-0.3304 (-1.433, 0.7578)	-0.3903 (-1.537, 0.7464)	0.04066 (-0.9842, 1.073)	-0.107 (-1.285, 1.074)	0.4879 (-1.154, 2.221)	
1.087 (0.3979, 1.864)	0.3304 (-0.7578, 1.433)	CABG	-0.05837 (-0.3818, 0.264)	0.3709 (-0.1532, 0.9082)	0.2247 (-0.4473, 0.9072)	0.8076 (-0.3876, 2.188)	
1.148 (0.3826, 1.983)	0.3903 (-0.7464, 1.537)	0.05837 (-0.264, 0.3818)	EES	0.4306 (-0.1877, 1.057)	0.2832 (-0.4617, 1.04)	0.8652 (-0.2814, 2.211)	
0.7197 (-0.1613, 1.647)	-0.04066 (-1.073, 0.9842)	-0.3709 (-0.9082, 0.1532)	-0.4306 (-1.057, 0.1877)	PES	-0.1469 (-0.7678, 0.4729)	0.4399 (-0.8755, 1.905)	
0.8682 (-0.1073, 1.881)	0.107 (-1.074, 1.285)	-0.2247 (-0.9072, 0.4473)	-0.2832 (-1.04, 0.4617)	0.1469 (-0.4729, 0.7678)	SES	0.5882 (-0.7967, 2.112)	
0.2824 (-1.26, 1.7)	-0.4879 (-2.221, 1.154)	-0.8076 (-2.188, 0.3876)	-0.8652 (-2.211, 0.2814)	-0.4399 (-1.905, 0.8755)	-0.5882 (-2.112, 0.7967)	ZES	

BioES	**0.9567 (0.01152, 2.033)**	**-0.641 (-1.003, -0.293)**	-0.0982 (-0.5659, 0.3653)	-0.1277 (-0.6017, 0.3418)	0.0608 (-0.4646, 0.59)	0.1264 (-0.5473, 0.8067)	Revascularization
-0.9567 (-2.033, -0.01152)	BMS	**-1.596 (-2.623, -0.7295)**	**-1.054 (-2.118, -0.1309)**	**-1.082 (-2.116, -0.1973)**	-0.8956 (-1.975, 0.04512)	-0.832 (-1.994, 0.224)	
0.641 (0.293, 1.003)	**1.596 (0.7295, 2.623)**	CABG	**0.5432 (0.2455, 0.8497)**	**0.514 (0.2072, 0.8272)**	**0.7023 (0.3189, 1.097)**	**0.7689 (0.1983, 1.353)**	
0.0982 (-0.3653, 0.5659)	1.054 (0.1309, 2.118)	**-0.5432 (-0.8497, -0.2455)**	EES	-0.02982 (-0.4618, 0.4039)	0.1596 (-0.3316, 0.654)	0.2256 (-0.2644, 0.7221)	
0.1277 (-0.3418, 0.6017)	1.082 (0.1973, 2.116)	**-0.514 (-0.8272, -0.2072)**	0.02982 (-0.4039, 0.4618)	PES	0.1886 (-0.225, 0.6081)	0.2553 (-0.3963, 0.9129)	
-0.0608 (-0.59, 0.4646)	0.8956 (-0.04512, 1.975)	**-0.7023 (-1.097, -0.3189)**	-0.1596 (-0.654, 0.3316)	-0.1886 (-0.6081, 0.225)	SES	0.06595 (-0.6265, 0.7658)	
-0.1264 (-0.8067, 0.5473)	0.832 (-0.224, 1.994)	**-0.7689 (-1.353, -0.1983)**	-0.2256 (-0.7221, 0.2644)	-0.2553 (-0.9129, 0.3963)	-0.06595 (-0.7658, 0.6265)	ZES	
BioES	**-1.001 (-1.895, -0.1452)**	**-0.5382 (-0.7923, -0.2897)**	**-0.5147 (-0.8634, -0.1697)**	**-0.6938 (-1.086, -0.3051)**	**-0.7158 (-1.17, -0.2634)**	-0.2929 (-0.9653, 0.3897)	Death/MI/Stroke
1.001 (0.1452, 1.895)	BMS	0.4615 (-0.3563, 1.319)	0.4848 (-0.3656, 1.374)	0.3071 (-0.5049, 1.154)	0.285 (-0.5917, 1.191)	0.7091 (-0.3203, 1.772)	
0.5382 (0.2897, 0.7923)	-0.4615 (-1.319, 0.3563)	CABG	0.02384 (-0.2147, 0.2622)	-0.1551 (-0.4557, 0.1429)	-0.1771 (-0.5554, 0.199)	0.2453 (-0.3767, 0.8807)	
0.5147 (0.1697, 0.8634)	-0.4848 (-1.374, 0.3656)	-0.02384 (-0.2622, 0.2147)	EES	-0.1792 (-0.5603, 0.2039)	-0.2009 (-0.6472, 0.2449)	0.2222 (-0.3544, 0.8121)	
0.6938 (0.3051, 1.086)	-0.3071 (-1.154, 0.5049)	0.1551 (-0.1429, 0.4557)	0.1792 (-0.2039, 0.5603)	PES	-0.02207 (-0.4051, 0.3617)	0.401 (-0.2901, 1.101)	
0.7158 (0.2634, 1.17)	-0.285 (-1.191, 0.5917)	0.1771 (-0.199, 0.5554)	0.2009 (-0.2449, 0.6472)	0.02207 (-0.3617, 0.4051)	SES	0.4237 (-0.3051, 1.162)	
0.2929 (-0.3897, 0.9653)	-0.7091 (-1.772, 0.3203)	-0.2453 (-0.8807, 0.3767)	-0.2222 (-0.8121, 0.3544)	-0.401 (-1.101, 0.2901)	-0.4237 (-1.162, 0.3051)	ZES	

Figure legends

Central Picture: Different stent generations vs. CABG for unprotected left main disease (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents)

Figure 1. Network plot of relevant studies. Circles represent each revascularization strategy as a node and lines represent the direct comparisons. The extent of circle indicates the number of patients receiving each revascularization strategy and the line thickness indicates the number of studies included in each comparison (Bio-ES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents)

Figure 2. Network meta-analysis estimates (expressed as incidence rate ratio, IRR, with relative 95% Credible interval, CrI) for different stent generations (CABG as comparator) (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents)

Figure 3. Network meta-analysis estimates (express as incidence rate ratio, IRR, with relative 95% Credible interval, CrI) for individual stent types (CABG as comparator). (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PCI:

percutaneous coronary intervention; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents)

Figure 4. Pairwise pooled and subgroup meta-analysis according to different stent generations for the composite of death/MI/stroke (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents).

Figure 5. Pairwise pooled and subgroup meta-analysis according to different stent generations for repeat revascularization (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stents; SES: sirolimus-eluting stents; ZES: zotarolimus-eluting stents).

Supplementary Figure 1. Flow diagram of study selection. CABG = coronary artery bypass graft surgery; CENTRAL = the Cochrane Central Register of Controlled Trials; LMD = left main disease; PCI = percutaneous coronary intervention; RCT: randomized controlled trials

Supplementary Figure 2. Median treatment effect and the 95% credible interval (for each type of stents compared to CABG) across Syntax score values for the composite of death/MI/stroke (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent)

Supplementary Figure 3. Median treatment effect and the 95% credible interval (for each type of stents compared to CABG) across Syntax score values for repeat revascularization (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent)

Supplementary Figure 4. Comparison of direct and indirect estimates to assess inconsistency (BioES: biolimus eluting stent; BMS: bare metal stent; CABG: coronary artery bypass grafting; EES: everolimus eluting stent; MI: myocardial infarction; PCI: percutaneous coronary intervention; PES: paclitaxel-eluting stent; SES: sirolimus-eluting stent; ZES: zotarolimus-eluting stent